VERMONT

Office of Vermont Health Access

Therapeutic Review
Buprenorphine and Buprenorphine/naloxone

Overview/Summary

Buprenorphine (Subutex®) and buprenorphine/naloxone (Suboxone®) are available in sublingual dosage form and are Food and Drug Administration (FDA) approved for the treatment of opioid dependence.[1] According to the Drug Addiction Treatment Act of 2000 (DATA 2000), the ability to prescribe buprenorphine or buprenorphine/naloxone for the maintenance or detoxification of opioid dependence is limited to physicians who have obtained a waiver and a unique Drug Enforcement Agency (DEA) number beginning with an X.[2] The requirements for this waiver include but are not limited to: specialization in addiction psychiatry, completion of an eight hour certification program and the ability to refer addiction treatment patients for appropriate counseling and other non-pharmacologic therapies.[2] Although buprenorphine and buprenorphine/naloxone have been studied in pain management and depression, neither of these sublingual products holds an FDA approval for these indications and their use for these indications will not be discussed within this review.[3]

Buprenorphine is a partial opioid agonist at the μ-opioid receptor (associated with analgesia and dependence) and an antagonist at the κ-opioid receptor (related to dysphoria).[1] Compared to full opioid agonists, partial agonists bind to the μ-opioid receptor at a higher degree while activating the receptor to a lesser degree. Partial opioid agonists reach a ceiling effect at higher doses and will displace full opioid agonists from the μ-opioid receptor. Although buprenorphine is associated with significant respiratory depression when used intravenously, or by patients with concomitant benzodiazepine or alcohol abuse, it is associated with a lower abuse potential, a lower level of physical dependence and is safer in overdose when compared to full opioid agonists.[4] During buprenorphine administration, opiate-dependent patients experience positive subjective opioid effects but not the euphoric effects that may contribute to opiate abuse.

Naloxone, an antagonist at the μ-opioid receptor, has measurable blood levels following sublingual buprenorphine/naloxone administration. However, due to naloxone's low oral bioavailability, there are no significant physiological or subjective differences when compared to the administration of buprenorphine alone.[1] Following intramuscular or intravenous administration, buprenorphine/naloxone is associated with symptoms of opiate withdrawal and dysphoria which is caused by a stronger affinity of naloxone for the opiate receptor compared to buprenorphine.[1] Therefore, the addition of naloxone to buprenorphine results in a decreased risk of diversion compared to buprenorphine monotherapy.

The United States Substance Abuse and Mental Services (SAMHSA) Clinical Guideline for the Use of Buprenorphine in the Treatment of Opioid Addiction recommends the use of buprenorphine/naloxone for the induction, stabilization and maintenance phases of opiate addiction treatment for most patients.[4] This guideline also notes that buprenorphine alone should be used for pregnant patients and for the induction therapy of patients who are transitioning from methadone treatment.[4] Transitioning patients to buprenorphine/naloxone as early as possible to minimize potential diversion associated with buprenorphine monotherapy is also reccomended.[3] Clinical trials comparing buprenorphine, both as monotherapy and in combination with naloxone, have demonstrated a significantly lower rate of positive thrice-weekly urine samples for non-study opioids compared to placebo[1]. When compared to opioid dependence treatment with methadone, treatment with buprenorphine and buprenorphine/naloxone offers the advantage of administration without enrollment in an addiction treatment program at a specialized

clinic. This flexibility in administration potentially allows more patients to be treated for opiate addiction than previously possible.[4] However; buprenorphine has been shown to be less effective in retaining patients in treatment compared to methadone and is significantly more expensive.[5]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single Entity Products		
Buprenorphine (Subutex®)	Outpatient partial opioid agonist	-
Combination Products		
Buprenorphine/naloxone (Suboxone®)	Outpatient partial opioid agonist	-

Indications

Table 2. Food and Drug Administration (FDA) Approved Indications[1]

Generic Name	Treatment of opioid dependence
Single Entity Product	
Buprenorphine	✔
Combination Product	
Buprenorphine/naloxone	✔

In addition to their FDA approved indications buprenorphine and buprenorphine/naloxone have been used off-label for pain management and depression.

Pharmacokinetics

The inter-patient variability in the sublingual absorption of buprenorphine and naloxone is wide; however the variability within subjects is low. Buprenorphine and naloxone are approximately 96% and 45% protein bound, respectively. Buprenorphine and naloxone undergo both N-dealkylation and glucuronidation. Additionally, naloxone undergoes reduction of the 6-oxo group. The N-dealkylation of buprenorphine is mediated by the P450 3A4 isoenzyme.

Table 3. Pharmacokinetics[1]

Drug	Absorption	Metabolism	Active Metabolites	Excretion (%)	Half-Life (hours)
Buprenorphine	Wide inter-patient variability	N-dealkylation and glucuronidation	Yes; norbuprenorphine (via N-dealkylation)	Urine:30 Feces:69	37
Naloxone	Wide inter-patient variability	Glucuronidation, N-dealkylation, and reduction	Yes; naloxone 3-glucuronide (via glucuronidation)	Primarily in the urine	1.1

Clinical Trials

In a double-blind, placebo and active controlled study, 326 patients 18-59 years of age who met the diagnostic criteria for opiate dependence and were seeking opiate-substitution pharmacotherapy were randomized to either buprenorphine/naloxone 16 mg/4 mg daily, buprenorphine 16 mg per day or placebo. The percentage of urine samples that were negative was significantly higher for both buprenorphine/naloxone and buprenorphine than placebo.[6] Other similar trials have demonstrated similar results. Overall these agents have been administered in conjunction with psychosocial counseling as part of a comprehensive addiction program and have found to be effective.

Clinical trials that have reported safety end points report that there is little difference in the adverse events seen with either buprenorphine alone or the combination buprenorphine/naloxone product. This may be directly related to the low oral bioavailability of naloxone.

Table 4. Clinical Trials

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ling et al[7] Buprenorphine 1, 4, 8 or 16 mg/day dissolved in 30% ethyl alcohol	DB, MC Men and women, average age of 36, that met the DSM-III criteria for opioid dependence and had used opioids daily during the previous 6 months	N=736 16 weeks	Primary: Safety and efficacy as measured by retention in treatment, illicit opioid use and opioid craving Secondary: Not reported	Primary: 51% of the patients completed the 16 week study. Completion rates varied by dosage group as follows: 40% for the 1 mg group, 51% for the 4 mg group, 52% for the 8 mg group, and 61% for the 16 mg group. The 16 mg group had significantly more patients with 13 consecutive negative urines than both the 1 mg group (P<0.001) and the 4 mg group (P<0.006). Significantly higher craving scores were observed for the 1 mg group compared to the 8 mg group at week 4 (P<0.01), 8 (P<0.01) and 12 (P=0.04), but not at week 16 (P=0.15). Secondary: Not reported
Lintzeris N[8] Buprenorphine SL tablets titrated to achieve comfortable withdrawal at the following total daily dose range: 4-8 mg on day 1, 0-16 mg on days 2-4, 0-8 mg on day 5 and 0 mg on days 6-8	OL Opioid dependent participants aged 18 or older with an opiate positive urine screen on assessment	N=18 8 days	Primary: Severity of withdrawal experience as measured by VAS scale Secondary: Measure of patient satisfaction with buprenorphine treatment, satisfaction with dosing regimen by Likert scale, drug use during the withdrawal episode, positive urine drug	Primary: The mean expected withdrawal severity as measured by VAS scale was 28 at intake. The mean experienced withdrawal severity was significantly lower compared to baseline (16±12, 95% CI, -2 to -26; P<0.05). Secondary: Patients were asked to identify positive and negative aspects of treatment (P values not reported); • 79% reported no, minimal or mild withdrawal symptoms • 57% reported feeling normal and being able to perform daily activities • 36% reported reduced or no cravings for heroin use • 29% reported being psychologically comfortable during withdrawal • 7% reported dissatisfaction with inconvenience of daily dosing • 7% reported that the dosing interval was too short • 7% identified sleep disturbance

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			screen and adverse events	• 57% reported side effects • 36% did not report any negative aspects of treatment The majority of patients rated the adequacy of their doses as "about right" on the Likert scale (11 of 14 patients). 3 subjects rated their doses as "too low" (*P* value not reported). Over the 8 days of treatment, 5 patients (28%) reported no drug use, 5 patients (28%) reported drug use on 1 day, 2 patients (11%) reported drug use on 2 days, 3 patients (17%) reported drug use on 3 or more days and data was unavailable for the remaining 3 patients (*P* values not reported). There were fewer patients with a positive urine screen for opiates (5 patients) at day 5 compared to those with negative opiate urine screen (9 patients, 50% of total sample and 60% of patients in treatment). On days 7-8, there were an equal number of patients with positive and negative opiate urine screens (4 patients, 22% of the sample, 29% of patients in treatment). Four patients were no longer in treatment and six reported heroin use (*P* values not reported). 16 patients reported adverse events. The most common were headache (50%), sedation (28%), nausea, constipation, and anxiety (21%).
Kornor H et al[9] Buprenorphine flexible daily dosing to a maximum dose of 16 mg daily	OL Opiate-dependent patients aged 22 years and older willing to enroll in a 9-month buprenorphine program	N=75 9 months	Primary: Self reported opioid abstinence in program completers and non-completers Secondary: Difference in number of days in within 30 days prior to follow up interview, in which the following	Primary: More program completers compared to non-completers reported abstinence from opioids during the 30 days prior to the follow-up, a difference that was not significant (7 vs 2; *P*=0.16). Secondary: Completers were employed for a higher number of days than non-completers at follow up (9 vs 2, respectively; *P*=0.012). There were no statistically significant differences between the two groups with regard to other psychosocial variables and substance use (*P* values not reported).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			occurred: heavy drinking, street opioid use, sedative, amphetamine, cannabis, polysubstance and intravenous use, employment, illegal activities, psychiatric problems and medical problems	There was a higher rate of abstinence from street opioids in the agonist therapy group (agonist therapy during the last 30 days) (24 of 37), compared to the no-agonist therapy group (9 of 31; *P*=0.003). The agonist therapy group had spent fewer days using street opioids (*P*<0.001), using two or more substances (*P*<0.038), injecting substances (*P*<0.007) and engaging in illegal activities (*P*<0.001) compared to the no-agonist group. The agonist therapy group had also been employed for a higher number of days (*P*=0.046). There was no difference between the two groups in health problems, heavy drinking and use of sedatives, amphetamine and cannabis (*P* values not reported).
Bickel et al[10] Buprenorphine maintenance dose (range from 4 mg/70 kg to 8 mg/70 kg) SL every 24 hours vs double maintenance dose SL every 48 hours vs triple maintenance dose SL every 72 hours Maintenance dose was administered to subjects for 13 consecutive days prior the initiation of the above dosing schedules.	DB, PC Individuals 18 years of age or older in good health, met DSM-III criteria for opioid dependence and FDA qualification criteria for methadone treatment	N=16 ~80 days	Primary: Self-report measures (i.e., visual analog scales and adjective rating scales) and observer measures Secondary: Not reported	Primary: Overall, there were no statistically significant differences among the different dosing schedules in any of the outcome measures including opioid agonist and withdrawal effects observed during the study (*P* values not reported). Significant differences were observed in some of the measures (i.e., percent identifications as placebo, percent identification as greater than maintenance dose, ARCI subscales) when comparing the daily maintenance dosing to those measures obtained 24, 48 and 72 hours following dosing schedules. Secondary: Not reported

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Petry et al[11] Buprenorphine maintenance dose (ranged from 4-8 mg/kg) SL every 24 hours vs double maintenance dose SL every 48 hours vs triple maintenance dose SL every 72 hours vs quadruple maintenance dose SL every 96 hours Subjects were administered 10 days of their daily SL maintenance dose to ensure stabilization.	DB, PC, XO Patients >18 years of age, in good health, met DSM-III criteria for opioid dependence and met FDA criteria for methadone treatment	N=14 ~43 days	Primary: Subjective opioid agonist and withdrawal effects Secondary: Not reported	Primary: There were no statistically significant differences among the different dosing schedules in any of the outcome measures, including subjective opioid agonist and withdrawal effects (*P* values not reported). When patients received quadrupled doses, there were no significant increases observed in opioid agonists effects compared to their usual maintenance dose (*P* values not reported). Subjects did report some differences in withdrawal effects (i.e., VAS, ARCI subscales) as the time between buprenorphine doses increased, but the clinical significance of these differences may be limited. Secondary: Not reported
Kakko et al[12] Buprenorphine 16 mg SL QD vs buprenorphine 6 day SL taper (8 mg for 2 days, 4	PC, RCT Opioid dependant individuals greater than 20 years of age, seeking admission for medically-assisted heroin withdrawal	N=40 1 year	Primary: 1 year retention in treatment Secondary: ASI	Primary: 1 year retention was significantly higher in the buprenorphine QD group compared to the taper/placebo group (RR, 58.7; 95% CI, 7.4 to 467.4; *P*=0.001). Secondary: The buprenorphine QD group had a significant reduction in ASI scores over time from baseline (*P*<0.0001).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg for 2 days, 2 mg for 2 days) followed by placebo	and who had a history of heroin dependence (as defined by the DSM-IV criteria) for at least a year			
Assadi et al[13] Experimental protocol: Buprenorphine 12 mg IM in 24 hours vs Conventional protocol: buprenorphine taper IM over 5 days (3 mg for 2 days, 2.7 mg for 1 day, 1.2 mg for 1 day and 0.6 mg for 1 day) Authors reported that buprenorphine SL is two thirds as potent as IM so 32 mg SL is equivalent to 18 mg IM.	DB, PG, RCT Subjects between the ages of 18 and 60 years who met the DSM-IV criteria for opioid dependence	N=40 10 days	Primary: Days of retention in treatment and rates of successful detoxification Secondary: SOWS and OOWS	Primary: There were no significant differences among the treatment protocols in the average number of days the subjects stayed in the study (experimental group: 9.5±1.8 days vs the conventional group: 9.8±0.9 days; *P*=0.52). There were no significant differences in the rates of successful detoxification among the treatment protocols; 18 subjects (90%) in each group were detoxified successfully (*P* value not reported). Secondary: There was not a significant difference demonstrated in mean overall SOWS scores between the two treatment protocols (experimental group: 9.0±6.6 vs the conventional group: 9.3±5.2; *P*=0.86). There were no significant differences found between the treatment protocols with regard to OOWS scores of the main effect of treatment (*P*=0.81), main effect of time (*P*=0.60) or treatment-time interactions (*P*=0.56).
Schottenfeld et al[14] Buprenorphine 16 mg/70 kg SL QD vs buprenorphine 34 mg/70 kg SL on Fridays and Sundays and 44 mg/70 kg	DB, RCT Patients who met FDA criteria for methadone maintenance, had a urine toxicology test positive for opioids, and met the DMS-IV criteria	N=92 12 weeks	Primary: Retention, 3 times per week urine toxicology tests and weekly self-reported illicit drug use Secondary: Not reported	Primary: There was no difference in percentage of subjects who completed the 12 weeks of treatment between the two groups (76.6% vs 71.1%; *P* value not reported). There was also no statistical difference observed between the two treatment groups in the average number of weeks in treatment (11.0±4.0 and 11.2±3.7, respectively; *P*=0.64). A significant decline in the proportion of opioid-positive urine tests was observed during the study (*P*<0.001), but there was no statistical difference between the two treatment groups (57% in the QD group vs

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
SL on Tuesdays There was a 3 day buprenorphine induction phase prior to randomization.	for opioid dependence			58% in the TIW group; *P*=0.84). A significant decline in the number of self-reported days per week of heroin use was observed during the study (*P*<0.001), but there was no statistical difference between the two treatment groups (1.3±0.23 in the QD group vs 1.7±0.22 in the TIW group; *P*=0.27). Secondary: Not reported
Amass et al[15] Buprenorphine/naloxone SL tablets for a total of 4 mg/1 mg on day 1 followed by another 4 mg/1 mg on day 1 unless the patient displayed agonist effects; escalated to 16 mg/4 mg on day 3 and tapered by 2 mg buprenorphine/day to 2 mg/0.5 mg by day 13	DB, MC, OL, RCT Opiate dependent patients aged 15 years and older experiencing withdrawal symptoms who requested medical treatment for the symptoms	N=234 13 days	Primary: Treatment compliance and retention Secondary: Ancillary medications administration rate and adverse effects	Primary: Of the 234 patients on buprenorphine/naloxone, all of the patients took the first dose and most patients received the 2nd day 1 dose (82.9%), the doses on days 2 and 3 (90.1%), and the majority of doses over the entire treatment course (10.5±3.8 of the 13 possible doses; 80.7%). 68% of patients completed the entire detoxification program (*P* values not reported). Secondary: The majority of patients (80.3%) were treated with ancillary medications for an average of 2.3 withdrawal medications. The most commonly treated symptoms were insomnia (61.5%), anxiety and restlessness (52.1%) and bone pain and arthralgias (53.8%). 61% of adverse events were expected events associated with drug relapse; however the specific adverse events were not reported.
Fudal et al[6] Phase I Buprenorphine 16 mg daily vs buprenorphine/naloxone 16 mg/4 mg daily vs	MC, PC, RCT with OL phase Men and women, ages 18-59, who met the diagnostic criteria for opiate dependence according to the DSM-IV who were seeking opiate-	Phase I N=326 Phase II N=472 52 weeks	Primary: Efficacy measured by percentage of urine samples negative for opiates and the subjects' self reported craving for opiates Secondary: Subjects' and	Primary: The percentages of urine tests that were opiate-negative were 17.8% in the combined-treatment group and 20.7% in the buprenorphine group, as compared with 5.8% in the placebo group (*P*<0.001 for both comparisons). For each of the four study weeks, the mean scores for opiate craving in the combined-treatment and buprenorphine groups were significantly lower than those in the placebo group (*P*<0.001 for both comparisons each week).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo Phase II Buprenorphine 8-12 mg for 2 days, then buprenorphine/naloxone 24 mg/6 mg daily	substitution pharmacotherapy		clinicians' impressions of overall status and adverse medical events	Secondary: Each week scores for subject's and clinicians' global impression were significantly higher in both the combined treatment group and buprenorphine alone treatment group than those in the placebo group (P<0.001 for both comparisons each week). The overall rate of adverse events did not differ significantly among the groups (78% in the combined treatment group, 85% in the buprenorphine only group, and 80% in the placebo group). The only adverse events that showed a significant difference in occurrences between treatment groups and placebo were withdrawal syndrome, constipation, and diarrhea. (P=0.008, P=0.03, and P=005 respectively), with the withdrawal syndrome and diarrhea occurring more frequently in the placebo group and constipation occurring more frequently in the treatment group.
Harris et al[16] Buprenorphine (solution) 4, 8, 16 and 32 mg SL administered as single dose each with washout periods between doses or buprenorphine (tablet) 16 mg SL as a single dose or buprenorphine/naloxone (tablet) 4 mg/1 mg, 8 mg/2 mg or 16 mg/4 mg SL as a single dose	RCT, XO Healthy volunteers aged 21 to 45 years and within 15% of ideal body weight for height and who were occasional but not dependant illicit opioid users	N=20 Duration not specified Pharmaco-dynamic effects were measured for 48-72 hours after administration	Primary: Plasma buprenorphine, norbuprenorphine and naloxone concentrations and pharmacodynamic effects Secondary: Not reported	Primary: Dose-adjusted AUC-time curve for buprenorphine 32 mg solution, buprenorphine 16 mg tablet and buprenorphine/naloxone 16 mg/4 mg tablet were only 54±16%, 70±25% and 72±17%, respectively, of that of the 4 mg dose of the solution or table (P=0.0001). There was no statistical difference in physiological effects such as heart rate, blood pressure, rate-pressure product, respiratory rate and pulse oximetry between the different doses in either experiment with the exception of pupil restriction. Pupils were still constricted at 48 hours after the volunteers took the solution doses and a dose response effect was observed (P<0.01). Volunteers in the solution group, but not those in the tablet group, rated global intoxication significantly higher following administration of the 32 mg SL solution than after the 4 and 8 mg doses (P<0.01), but not compared with the 16 mg dose (P value not reported). Drug liking and good drug effect ratings increased in all experiments compared to baseline. In the solution group, volunteers reporting drug

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				liking across time was significantly higher with 4 mg compared to 8 mg (*P*<0.04), 16 mg (*P*<0.04) and 32 mg (*P*<0.01) doses. Although not statistically significant, drug liking for the tablet increased with increasing dose. There was no significant difference in good drug effect and opioid agonist ratings between the solution and tablet (*P* value not reported). Secondary: Not reported
Correia et al[17] Buprenorphine/naloxone 8 mg/2 mg SL QD vs buprenorphine/naloxone 16 mg/4 mg SL QD vs buprenorphine/naloxone 32 mg/8 mg SL QD After 2 weeks on each maintenance dose, participants underwent challenge sessions consisting of IM hydromorphone.	DB, RCT Adult volunteers with active opioid dependence as confirmed through self-report, urinalysis and observation and met DSM-IV criteria of current opioid (heroin) dependence	N=8 11 weeks	Primary: Opioid blockade and withdrawal effects Secondary: Not reported	Primary: Although substantial, all three buprenorphine doses provided incomplete blockade against opioid agonist effects for 98 hours based on the number of subjective (i.e., drug effects) and physiologic (i.e., blood pressure, heart rate) effects measured. *P* values for most measures were >0.05 with the exception of pupil diameter and oxygen saturation. The 32 mg/8 mg dose produced less constricted pupils compared to the 8 mg/2 mg dose (*P*≤0.05). The 8 mg/2 mg dose produced lower oxygen saturation as compared to the 16 mg/4 mg dose (*P*≤0.05). There were no significant differences regarding symptoms of withdrawal among the study doses (*P*>0.05). As time since the last dose increased, so did the number of mild effects reported (*P* value not reported). Secondary: Not reported
O'Connor et al[18] Buprenorphine 3 mg SL on days 1 through 3, plus clonidine 0.1-0.2 mg every	DB, RCT Participants 18 to 50 years of age who were opioid	N=162 8 days	Primary: Successful detoxification Secondary:	Primary: There were no significant differences in rates of successful detoxification among treatment groups; 65% in the clonidine groups vs 81% in the clonidine with naltrexone group (*P*=0.06) vs 81% in the buprenorphine group (*P*=0.07).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
4 hours as needed to control withdrawal symptoms plus naltrexone 25 mg on day 4 and 50 mg on day 5 vs clonidine 0.1-0.2 mg every 4 hours as needed to control withdrawal symptoms plus naltrexone 12.5 mg on day 1, 25 mg on day 2 and 50 mg on day 3 vs clonidine 0.1-0.2 mg every 4 hours as needed to control withdrawal symptoms	dependant		Treatment retention and withdrawal symptoms	Secondary: There were no significant differences in rates of retention among treatment groups; 65% in the clonidine groups vs 54% in the clonidine with naltrexone group vs 60% in the buprenorphine group (*P* values not reported). There was a significantly lower mean overall withdrawal symptoms score observed in the buprenorphine group (13.2±8.4) compared to the clonidine (17.8±10.3; *P*=0.01) and the clonidine plus naltrexone group (17.6±9.3; *P*=0.016).
Marsch et al[19] Buprenorphine SL tablets dosed 6 mg daily (if patient weight <70 kg and/or opiate use was the equivalent of 1 to 3 bags of heroin) or 8 mg daily (if >70 kg and/or opiate use was greater than the equivalent of 3 bags of heroin); decreased by 2 mg every 7 days in addition to placebo	DB, DD, PG, RCT Self-referred adolescents aged 13-18 years who met DSM-IV criteria for opiate dependence	N=36 28 days	Primary: Percentage of patients retained in treatment, opiate abstinence as measured by percentage of negative scheduled urine opiate samples and drug related HIV risk behavior as measured by HRBS scale	Primary: Significantly more patients were retained in treatment for the duration of the detoxification period with buprenorphine compared to clonidine (72% vs 39%; *P*=0.04). Buprenorphine was associated with a higher percentage of patients with opiate-negative urine samples during the entire detoxification compared to clonidine (64% vs 32%; *P*=0.01). There was a significant decrease in HIV risk behavior from treatment intake to the end of the first week (*P*=0.05). However, there was no difference in decrease in drug-related risk composite scores between the buprenorphine and the clonidine groups (*P*=0.86).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
transdermal patch for the duration of the study vs clonidine 0.1 mg transdermal patch on day 1; a second patch could be added on day 2 and worn for days 2-6, and a third patch on day 4 and worn for days 4-6, followed by 0.2 mg patch for days 7-14, 0.1 mg patch for days 14-21, and a 0 mg placebo patch thereafter in addition to placebo sublingual tablet for the study duration			Secondary: Physiological signs of opiate effects including pupil constriction, self reports of drug effects as measured by adjective scale, effect of drug as measured by VAS scale, psychomotor performance as measured by Digit Symbol Substitution Test, other drug use as measured by urinalysis and percentage of patients initiating naloxone post detoxification	Secondary: There was a significantly larger reduction of pupil radius from predosing to postdosing of buprenorphine compared the clonidine group (P<0.001).There was a significant reduction in pupil size from baseline in the buprenorphine group (P<0.001) however there was no reduction seen in the clonidine group (P=0.36). There was a decrease in withdrawal scores on the adjective rating scale from predosing to postdosing among participants in both treatment groups during the first week (P<0.001). There was no difference in decrease in the sum of withdrawal scores between the buprenorphine group and the clonidine treatment group (P=0.64). There was a significant change in sum of agonist scores on the adjective rating scale from predosing to postdosing during the first week (P<0.001).The sum of agonist scores from predosing to postdosing significantly increased in the buprenorphine group (P=0.005) and significantly decreased in the clonidine group (P=0.02). Buprenorphine-treated patients reported significant increases on measures of drug-related high, drug effect, good effect, and drug liking (P values <0.01), however clonidine-treated patients reported no significant changes on these measures from predosing to postdosing during the first week (P values >0.05). Clonidine-treated patients reported significant increases on the measure of bad effect (P=0.008), however buprenorphine-treated patients reported no change on this measure (P=0.51). Participants in both groups reported decreases on the measure of sick from predosing to postdosing during the first week (P<0.001), and there was no difference between the two treatment groups (P=0.07). There was no difference in percentage correct on the Digit Symbol Substitution Test across both treatment groups (P=0.07) and no change from predosing to postdosing during the first week for participants in either group (P=0.35).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was no difference between the buprenorphine group and the clonidine group in terms of urine samples negative for cocaine (87% vs 85%, respectively), benzodiazepines (90% vs 93%, respectively) and marijuana (36% vs 29%, respectively; *P* values not reported). At the conclusion of the detoxification, a larger amount of patients in the buprenorphine group (61%) compared to the clonidine group (5%) participated in the naltrexone phase of the study.
Gibson et al[20] Buprenorphine (dosing not specified) vs methadone(dosing not specified)	DB, MC, RCT Heroin-dependent patients aged 18 years and older who lived within commuting distance of the clinic	N=405 91 day treatment period followed by a 10 year longitudinal follow-up	Primary: Effects of opioid maintenance treatment on mortality rate Secondary: Difference between two treatment groups in exposure to opioid maintenance treatment episodes greater than 7 days and 14 days, causes of death and effects of race, level of heroin dependence and age on mortality rate	Primary: There were 30 deaths in the follow-up period (16 in the buprenorphine group vs 14 in the methadone group). Each additional treatment episode of methadone or buprenorphine treatment lasting longer than 7 days reduced the risk of death on average by 28% (95% CI, 7% to 44%) Secondary: There was no significant difference over the follow-up period in percentage time exposure to opioid maintenance treatment episodes greater than 7 days (*P*=0.52) between the buprenorphine and methadone groups. The methadone treatment group was significantly more likely to spend greater percentage follow-up time in methadone treatment episodes longer than 14 days (*P*<0.0001).The buprenorphine group was also significantly more likely to spend longer time in buprenorphine treatment episodes longer than 14 days (*P*<0.0001). Drug overdose or related complications were the most common cause of death in the 30 deceased participants (40% of the deaths). Aboriginal or Torres Strait Islander patients had 5.32 times the risk of death of non-Aboriginal or Torres Strait Islander participants (95% CI, 1.89 to 14.95). The risk of death among participants using more heroin at baseline during follow-up was 12% lower (95% CI, 5% to 18%; *P* value not reported) than less frequent heroin users at baseline. The risk of death during the follow-up period was 11% lower for older

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				patients (95% CI, 2% to 19%) than younger participants who were randomized to methadone.

Drug regimen abbreviations: IM=intramuscular, QD=daily, SL=sublingual, TIW=three times weekly
Study abbreviations: DB=double-blind, DD=double dummy, MC=multi-center, PC=placebo-controlled, OL=open label, PG=parallel group, RCT=randomized controlled trial, XO=crossover
Miscellaneous abbreviations: ARCI=Addiction Research Center Inventory, ASI=addiction severity index, AUC=area under the curve, DSM=Diagnostic and Statistical Manual of Mental Disorders, FDA=food and drug administration, HIV=Human immunodeficiency virus, HRBS=HIV Risk Behavior Scale, OOWS=Objective Opiate Withdrawal Scale, chlorpromazine, alcohol group (sedation group), RR=relative risk, SOWS=Subjective Opiate Withdrawal Scale, VAS=visual analog scale

Special Populations

In addition to the patient populations outlined in Table 5, buprenorphine and buprenorphine/naloxone should be used with caution in patients with severe pulmonary function impairment, myxedema or hypothyroidism, adrenal cortical insufficiency, central nervous system depression or coma, toxic psychosis, prostatic hypertrophy or urethral stricture, acute alcoholism, delirium tremens, kyphoscoliosis, biliary tract dysfunction, acute abdominal conditions or are considered debilitated. It should be noted that neonatal withdrawal has been reported in the infants of women treated with buprenorphine during pregnancy.[1]

Table 5. Special Populations[1]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal dysfunction	Hepatic dysfunction	Pregnancy Category	Excreted in Breast Milk
Buprenorphine and buprenorphine /naloxone	Safety and efficacy in children <16 years of age have not been established. Administer with caution in the elderly population.	No buprenorphine dosage adjustment required in renal dysfunction. Naloxone has not been studied in renal dysfunction.	Hepatic dose adjustment required.	C	Excreted in breast milk (% unknown).

Adverse Drug Events

Clinical trials have examined the safety of buprenorphine/naloxone and buprenorphine in opioid-dependent subjects. In a comparative 4 week study, few differences in adverse events between buprenorphine and buprenorphine/naloxone were observed.[1] Adverse events that were reported by at least 5% of the patients in the study are outlined in Table 6.

Table 6. Adverse Drug Events (≥5%) in a 4-week Study[1]

Adverse Event	Buprenorphine/Naloxone 16 mg/day N=107; N (%)	Buprenorphine 16 mg/day N=103; N (%)	Placebo N=107; N (%)
Body as a whole			
Asthenia	7 (6.5)	5 (4.9)	7 (6.5)
Chills	8 (7.5)	8 (7.8)	8 (7.5)
Headache	39 (36.4)	30 (29.1)	24 (22.4)
Infection	6 (5.6)	12 (11.7)	7 (6.5)
Pain	24 (22.4)	19 (18.4)	20 (18.7)
Pain abdomen	12 (11.2)	12 (11.7)	7 (6.5)
Pain back	4 (3.7)	8 (7.8)	12 (11.2)
Withdrawal syndrome	27 (25.2)	19 (18.4)	40 (37.4)
Cardiovascular System			
Vasodilation	10 (9.3)	4 (3.9)	7 (6.5)
Digestive System			
Constipation	13 (12.1)	8 (7.8)	3 (2.8)
Diarrhea	4 (3.7)	5 (4.9)	16 (15.0)
Nausea	16 (15.0)	14 (13.6)	12 (11.2)
Vomiting	8 (7.5)	8 (7.8)	5 (4.7)
Nervous System			
Insomnia	15 (14.0)	22 (21.4)	17 (15.9)

Adverse Event	Buprenorphine/Naloxone 16 mg/day N=107; N (%)	Buprenorphine 16 mg/day N=103; N (%)	Placebo N=107; N (%)
Respiratory System			
Rhinitis	5 (4.7)	10 (9.7)	14 (13.1)
Skin & Appendages			
Sweating	15 (14.0)	13 (12.6)	11 (10.3)

Contraindications / Precautions

Cases of acute and chronic hypersensitivity to buprenorphine have been reported. These products are contraindicated in patients with hypersensitivity to buprenorphine and buprenorphine/naloxone is also contraindicated in patients with hypersensitivity to naloxone.[1]

Respiratory depression, central nervous system depression and impairment of mental or physical abilities have been reported with the use of buprenorphine. Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in the addict population receiving buprenorphine. Buprenorphine can elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury. Orthostatic hypotension has also been reported in ambulatory patients using buprenorphine.[1]

Drug Abuse and Dependence

Buprenorphine and buprenorphine/naloxone are controlled as schedule III narcotics. Chronic administration of buprenorphine can produce dependence characterized by withdrawal upon abrupt discontinuation or rapid taper. Because it contains naloxone, buprenorphine/naloxone is highly likely to produce marked and intense withdrawal symptoms if misused parenterally by individuals dependent on opioid agonists (eg, heroin, morphine and methadone). Sublingually, buprenorphine/naloxone may cause opioid withdrawal symptoms in these people if administered before the agonist effects of the opioid have subsided.[1,21-22]

Drug Interactions

Dosage adjustments of buprenorphine may be necessary in patients receiving CYP 3A4 inhibitors such as azole antifungals, macrolide antibiotics and protease inhibitors. There have been reports of coma and death associated with the concomitant intravenous misuse of buprenorphine and benzodiazepines by addicts.[1,21-22]

Table 7. Drug Interactions[1]

Generic Name	Interacting Medication or Disease	Potential Result
Buprenorphine	Barbiturate Anesthetics (methohexital, thiamylal and thiopental)	The dose of thiopental required to induce anesthesia may be reduced in the presence of buprenorphine. Although apnea may be more common with this combination and drug actions may be additive, no additional precautions other than those routinely used in anesthesia appear necessary.
Buprenorphine	Benzodiazepines (alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, quazepam, temazepam and triazolam)	Concomitant administration results in an increased risk of sedation and life-threatening respiratory depression, especially with over dosage. Subjective and performance responses may also be altered; caution patients against driving or operating machinery while taking these agents.
Buprenorphine	Protease Inhibitors (amprenavir, atazanavir, darunavir, fosamprenavir,	Buprenorphine plasma concentrations may be increased and the $t_{1/2}$ prolonged, increasing the risk of adverse reactions (eg, respiratory

Generic Name	Interacting Medication or Disease	Potential Result
	indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir and tipranavir)	depression). Closely monitor respiratory function during buprenorphine administration and for a longer period than usual after stopping buprenorphine in patients receiving Protease Inhibitors. If the buprenorphine is administered continuously, it may be necessary to reduce the buprenorphine dose.

Dosage and Administration

Buprenorphine and buprenorphine/naloxone have a typical dosage range of 12 to 16 mg/day and are administered sublingually once daily. In situations where multiple tablets are administered at the same time, either all tablets may be placed at once or two tablets at a time may be placed under the tongue. In all cases the tablets should remain under the tongue until fully dissolved. If tablets are swallowed the bioavailability of the drug is reduced.[1] When used as indicated these agents have similar clinical effects and are interchangeable.

Buprenorphine/naloxone can be used for induction in patients dependent on short acting opioids and is the preferred agent for maintenance and in situations where administration is unsupervised. The maintenance phase usually averages 1-2 months.[1] During this time the recommended target dose is 16 mg per day with a range between 4-24 mg/day.[1,4] Doses should be adjusted in increments of 2-4 mg to suppress withdrawal symptoms. Although both gradual and abrupt discontinuation methods have been used, there have been no studies to evaluate the best method of dose taper at the end of treatment.

Table 8. Dosing and Administration[1]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single Entity Product			
Buprenorphine	Initial, 12-16 mg/day as a single daily dose during induction; maximum, 32 mg daily	Safety and efficacy in children <16 years of age have not been established.	Tablet: 2 mg 8 mg
Combination Product			
Buprenorphine/ naloxone	Initial, 12-16 mg/day as a single daily dose during maintenance; maximum, 32 mg daily	Safety and efficacy in children <16 years of age have not been established.	Tablet: 2 mg/0.5 mg 8 mg/2 mg

Other Key Facts

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
United States Substance Abuse and Mental Services (SAMHSA) Center for Substance Abuse Treatment: **Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction (2004)[4]**	• Buprenorphine/naloxone should be used for the induction, stabilization, and maintenance phases of treatment for most patients. • Induction doses should be administered as observed treatment; however, subsequent doses may be obtained with a prescription. • In most patients, buprenorphine/naloxone can be used for induction. If buprenorphine monotherapy is used, patients should be transitioned to buprenorphine/naloxone after no more than 2 days of treatment. If buprenorphine monotherapy is to be used for extended periods, the number of doses to be prescribed should be limited, and the use of the monotherapy formulation should be justified in the medical record.

Clinical Guideline	Recommendations
	• Buprenorphine/naloxone or buprenorphine should only be used in patients dependent on long-acting opioids who have evidence of sustained medical and psychosocial stability in conjunction with opioid treatment programs. In these patients, buprenorphine monotherapy should be utilized during the induction phase to avoid precipitation of withdrawal. • For patients taking methadone, the methadone dose should be tapered to ≤ 30 mg/day for ≥1 week and patients should have taken their last dose of methadone ≥ 24 hours prior to initiating buprenorphine induction. The first dose of buprenorphine should be 2 mg of the monotherapy formulation. If a patient develops signs or symptoms of withdrawal after the first dose, a second dose of 2 mg should be administered and repeated as needed to a maximum of 8 mg of buprenorphine on day 1. The decision to transfer a patient, exhibiting withdrawal symptoms, from methadone at doses >30 mg/day to buprenorphine should be based on a physician's judgment as there is insufficient data in this patient population. • Patients, who are experiencing objective signs of opioid withdrawal and whose last use of a short-acting opioid were, ≥12 to 24 hours prior, should be inducted using buprenorphine/naloxone. Patients should receive a first dose of 4 mg/1 mg to 8 mg/2 mg of the buprenorphine/naloxone combination. If the initial dose of the combination treatment is 4 mg/1 mg and opioid withdrawal symptoms subside but then return (or are still present) after 2 hours, a second dose of 4 mg/1 mg may be administered. The total amount of buprenorphine administered in the first day should not exceed 8 mg. • If patients do not exhibit withdrawal symptoms after the first day of induction, the patient's daily dose should be equivalent to the total amount of buprenorphine/naloxone (or buprenorphine) that was administered on day 1. Doses may be subsequently increased in 2 mg/0.5 mg to 4 mg/1 mg increments daily, if needed for symptomatic relief, with a target dose of 12 mg/3 mg to 16 mg/4 mg per day within the first week. • Patients experiencing withdrawal symptoms on day 2 should receive an initial dose of buprenorphine/naloxone equivalent to the total amount of buprenorphine administered on day 1 plus 4 mg/1 mg (maximum initial dose of 12 mg/3 mg). If withdrawal symptoms are still present 2 hours after the dose, an additional 4 mg/1 mg dose can be administered. The total dose on day 2 should not exceed 16 mg/4 mg. Continue dose increases on subsequent days as needed. • The stabilization phase begins when patients are free of withdrawal symptoms and cravings. Most patients will stabilize on daily doses of 16 mg/4 mg to 24 mg/6 mg; however doses up to 32 mg/8 mg daily may be required in some patients. • During stabilization, patients receiving maintenance treatment should be seen at least weekly. Once a stable buprenorphine dose is reached and toxicologic samples are free of illicit opioids, less frequent visits (biweekly or monthly) may be an option. Toxicology tests for illicit drugs should be administered at least monthly. • The longest phase of treatment is the maintenance phase which may be indefinite. Decisions to decrease or discontinue

Clinical Guideline	Recommendations
	buprenorphine should be based on a patient commitment to being medication-free and on physician judgment. • Patients treated for opiate withdrawal should receive psychosocial therapy (eg, individual or group counseling, self-help programs, and patient monitoring) and have their medical comorbidities managed effectively. • Buprenorphine monotherapy may be used for medically supervised withdrawal. • Detoxification in short-acting opioid addiction can be rapid (3 days), of moderate length (10-14 days) or long term (indefinite). Buprenorphine long term therapy may be more effective than rapid detoxification from short-acting opioid abuse. • In pregnant women methadone is currently the standard of care, however if this option is unavailable or refused by the patient buprenorphine may be considered as an alternative. Although the Suboxone® and Subutex® product information advise against use in breast-feeding, the effects on the child would be minimal and buprenorphine use in breast-feeding is not contraindicated in this patient population. • In adolescents and young adults buprenorphine is a useful option however, the practitioner should be familiar with the state laws regarding parental consent. • In geriatric patients the literature is lacking however due to differences in metabolism and absorption, additional care should be exercised when treating these patients. • In instances of polysubstance abuse, buprenorphine may not have a beneficial effect on the use of other drugs. Extra care should be employed in patients who abuse alcohol or benzodiazepines due to the potentially fatal interactions with buprenorphine. • Patients who need treatment for pain but not for addiction should be treated within the context of a medical or surgical setting and should not be transferred to an opioid maintenance program just because they have become physically dependant throughout the course of medical treatment. • Pain, in patients receiving buprenorphine for opioid addiction, should be treated with short-acting opioid pain relievers and buprenorphine should be held. Sufficient time for these medications to be cleared must allowed before restarting the buprenorphine. Patients with chronic severe pain may not be good candidates for buprenorphine because of the ceiling effect. • In patients recently discharged from controlled environments, intensive monitoring is required, and treating physicians may be called upon to verify and explain treatment regimens, to document patient compliance and to interact with the legal system, employers, and others. These patients may be candidates for buprenorphine treatment even if there is no current opioid abuse. The lowest dose possible of buprenorphine/naloxone should be used (2 mg/0.5 mg). • Opioid addiction in health care professionals requires specialized, extended care since opioid addiction is an occupational hazard.
Treatment Guidelines from The Medical Letter: **Drugs for Pain (2007)**[3]	• Partial agonists, like buprenorphine, have only a limited role in chronic pain management due to dose-related adverse events. • Partial agonists have a ceiling on analgesic effect and may precipitate withdrawal symptoms if administered to patients

Clinical Guideline	Recommendations
	dependent on full agonists. • There is a risk of dependence associated with partial agonists; however the risk is less than that of full agonists. • Buprenorphine is not available as an oral treatment for pain; however Suboxone® (buprenorphine/naloxone) and Subutex® (buprenorphine) are available as sublingual tablets and are approved for the treatment of opioid dependence. • Aspirin, acetaminophen, and non-steroidal anti-inflammatory drugs (NSAIDS) are recommended as first line agents for mild to moderate pain. • For moderate pain NSAIDS have been shown to be more effective than aspirin and acetaminophen, and may be equal to or greater than acetaminophen/opioid combination products or opioids administered via injection, at recommended doses. • Strong opioid full agonists are recommended as the first line treatment for severe pain. • Full opioid agonists generally have no ceiling effect and the dose may be increased as tolerated based on adverse effects. • Patients who do not respond to one opioid may respond to another. The choice of opioid should be based on adequate analgesia being provided with minimal adverse effects. • When frequent as-needed dosing with short–acting agents becomes inappropriate, use of long-acting agents is warranted. • Combination regimens, including opioids, non-opioids, and adjuvant analgesics, are useful for severe chronic pain.

Conclusions

Buprenorphine and buprenorphine/naloxone are treatment options for opiate dependent patients who are unable or unwilling to receive clinic-based methadone treatment.[4] Compared to methadone treatment, the partial agonist buprenorphine has the advantages of providing the positive subjective effects associated with opiate abuse and preventing withdrawal symptoms while removing the euphoria associated with further opiate abuse.[4] Buprenorphine is associated with a risk of respiratory depression, especially if injected or given concomitantly with benzodiazepines or alcohol, however these risks are less than that of traditional full opioid agonists due to the ceiling effect associated with partial agonist therapy.[4] Naloxone is an opiate antagonist and when used in combination with buprenorphine may help to prevent abuse by precipitating withdrawal and dysphoria when this combination product is inappropriately administered via injection.

Physicians prescribing buprenorphine for opiate dependency in an office-based treatment setting are required to complete a training program as outlined in the Drug Addiction Treatment Act of 2000 (DATA 2000).[2] According to The United States Substance Abuse and Mental Services (SAMHSA) guidelines, physicians should be aware of the potential for abuse and diversion of buprenorphine monotherapy and reserve maintenance buprenorphine monotherapy for patients who are pregnant or who have a documented allergy to naloxone.[4] Physicians should include buprenorphine as part of a total treatment plan including: counseling services, toxicologic evaluations for opioid abuse, management of comorbidities and close patient monitoring.[4] Sublingual buprenorphine and buprenorphine/naloxone are not indicated for the treatment of pain or depression, however it has been studied in both conditions. The treatment guidelines from The Medical Letter as noted above do address the use of buprenorphine for pain. However there is a lack of strong recommendations for its use compared to other appropriate agents.

Recommendations

Based on the information presented in the review above and cost considerations, no changes are recommended to the current approval criteria.

Suboxone® and Subutex® require prior authorization with the following approval criteria:

Suboxone®

- Diagnosis of opiate dependence confirmed (will not be approved for alleviation of pain).
  AND
- Prescriber has an DATA 2000 waiver ID number ("X-DEA license") in order to prescribe

Subutex®

- Diagnosis of opiate dependence confirmed (will not be approved for alleviation of pain).
  AND
- Prescriber has an DATA 2000 waiver ID number ("X-DEA license") in order to prescribe
  AND
- Patient is either pregnant (duration of PA will be one 1 month post anticipated delivery date)
  OR
- Patient has a documented allergic reaction to naloxone supported by medical record documentation. Allergic reaction should have been observed by a health care professional.

References

1) Suboxone/Subutex™ [package insert]. Hull, UK: Reckitt Benckiser Healthcare; 2006 Sept.
2) U.S. Department of Health and Human Services: Substance Abuse and Mental Health Services. Drug addiction treatment act of 2000 [Guideline on the internet] Washington, D. C.: U.S. Department of Health and Human Services [cited 2008 September 5] Available from: http://buprenorphine.samhsa.gov/data.html.
3) Medical Letter, Inc. Treatment guidelines from the Medical Letter: Drugs for Pain. 2007;5(56):23-32.
4) Center for Substance Abuse Treatment. Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction. Rockville (MD): Substance Abuse and Mental Health Services Administration (SAMHSA); DHHS Publication No. (SMA) 04-3939. 2004.
5) Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2003(2):CD002207.
6) Fudala PJ. et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. N Engl J Med. 2003;349:949-58.
7) Ling W. et al. Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. Addiction. 1998;93(4):475-86.
8) Lintzeris N. Buprenorphine dosing regime in the management of out-patient heroin withdrawal. Drug Alcohol Rev. 2002 Mar;21(1):39-45.
9) Kornor H, Wall H, and Sandvik L. Time-limited buprenorphine replacement therapy for opioid dependence: 2 year follow-up outcomes in relation to programme completion and current agonist therapy status .Drug and Alcohol Review. 2007 March;26:135-41.
10) Bickel WK, Amass L, Crean JP, Badger GJ. Buprenorphine dosing every 1,2, or 3 days in opioid-dependant patients. Psychopharmacology (Berl). 1999 Sep;146(2):111-8.
11) Petry NM, Bickel WK, Badger GJ. A comparison of four buprenorphine dosing regimens in the treatment of opioid dependence. Clin Pharmacol Ther. 1999 Sep;66(3):306-14.
12) Kakko J, Svanborg KD, Kreek MJ, Heilig M. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. Lancet. 2003 Feb 22;361(9358):662-8.
13) Assadi SM, Hafezi M, Mokri A, Razzaghi EM, Ghaelo P. Opioid detoxification using high doses of buprenorphine in 24 hours: A randomized, double blind, controlled clinical tiral. J Subst Abuse Treat. 2004 Jul;27(1):75-82.
14) Schottenfeld RS, Pakes J, O'Connor P, Chawarski M, Oliveto A, Kosten TR. Thrice-weekly versus daily buprenorphine maintenance. Biol Psychiatry. 2000 Jun 15;47(12):1072-9.
15) Amass L, Ling W, Freese TE, Reiber C, Annon JJ, Cohen AH et al. Bringing buprenorphine-naloxone to community treatment providers: the NIDA clinical trials network field experience.The American Journal on Addictions. 2004;13 Suppl 1:S42-66.
16) Harris DS, Mendelson JE, Lin ET, Upton RA, Jones RT. Pharmacokinetics and subjective effects of sublingual buprenorphine, alone or in combination with naloxone. Clin Pharmacokinet. 2004;43(5):329-40.
17) Correia CJ, Walsh SL, Bigelow GE, Strain EC. Effects associated with double-blind omission of buprenorphine/naloxone over a 98-h period. Psychopharmacology (Berl). 2006 Dec;189(3):297-306.
18) O'Connor PG, Carroll KM, Shi JM, Schottenfeld RS, Kosten TR, et al. Three methods of opioid detoxification in a primary care setting. Ann Intern Med. 1997 Oct 1;127(7):526-30.
19) Marsch LA, Bickel WK, Badger GJ, Stothart ME, Quesnel KJ, Stanger C, et al. Comparison of Pharmacological Treatments for Opioid-Dependent Adolescents. Arch Gen Psychiatry. 2005;62:1157-64.
20) Gibson A, Degemhardt L, Mattick RP, Ali R, White J O'Brien S. Exposure to opioid maintenance treatment reduces long term mortality. Addiction. 2008; 103(3):462-468.
21) Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2007 [cited 2007 May 5]. Available from: http://online.factsandcomparisons.com.
22) Alho H, Sinclair D, Vuori E, Holopainen A. Abuse liability of buprenorphine-naloxone tablets in untreated IV drug users. Drug Alcohol Depend. 2007 Apr 17;88(1):75-8. Epub 2006 Oct 19.